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10/588,792	10/26/2006	Hiroyuki Kamiya	2006_1315A	9531

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
12/13/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,792	KAMIYA ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *12,13 and 15-23* is/are pending in the application.

5a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *12, 13, 15, 16 and 23* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal brief filed on 9/26/2011, PROSECUTION IS HEREBY REOPENED. As set forth below. To avoid abandonment of the application, appellant must exercise one of the following two options:
(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,
(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.
A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Gary Benzion/
Supervisory Patent Examiner, Art Unit 1637

Status of claims

2. Applicants 'appeal brief filed on 9/26/2011 is acknowledged. Claims 12, 13, 15-23 are pending. Claims 17-22 remain withdrawn. Claims 12, 13, 15, 16 and 23 are active and were rejected under 103 over Zarling et al. and Moriya et al.

Response to Applicant's Appeal brief filed under 37 CFR 41.37

3. Appellant's argues the following points:

How would one of skill in the art know that only the + or the – stand would be more effective?

Appellant also states "Examiner has merely noted that it is possible to use single strand DNA to prepare a desired fragment. Why a skilled artisan would perform such extra steps, without use of impermissible hindsight in view of the claimed invention, is absent from the Examiner's statement.

Appellant also states "In the advisory action Examiner further indicates that the 10 fold improvement in conversion efficiency is obvious" and goes on to state "Examiner has merely shown that plus or minus strains can be made but has not articulated reasoning with some rational underpinning to support combination of single strain sense DNA fragment with the teachings of Zarling."

The examiner performed a search and found prior art that addresses all the above arguments. This new art is being used by the examiner to reject all the active claims. The new art Bilang et al. teaches performing homologous recombination in Nicotiana tabacum using single-stranded DNA fragment prepared by cleavage from a single-stranded circular DNA, and introducing said single-stranded DNA fragment into a cell, wherein said single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence. This newly cited art Bilang et al. teaches method recited in instant claim 12, 13 and 16. Bilang et al. do not teach where the target DNA sequence in the cell is a DNA sequence causing a disease due to one or more bases.

Liu et al. 2003 have reviewed the development and regulation of gene repair in eukaryotic and mammalian cells. This newly cited art is being used to make scope of enablement rejection in the rejection that follow. In view of new grounds of rejection are being introduced all the previous rejections over Zarling and Moriya et al. are withdrawn.

Claim Interpretation

4. Instant claim 12 is directed to "an in vitro base conversion method" of a DNA sequence, which is referred to as "homologous recombination" in prior art. Hence art teaching homologous recombination teaches an in vitro base conversion method.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12, 13, 15, 16 and 23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Base claim 14 is drawn to in vitro base conversion in target DNA using a single-stranded DNA sense fragment. The only description provided in the examples is conversion of a single base pair difference in a fragment of a gene inserted into a plasmid contained within *E. coli* cells. The plasmid was double-stranded. The specification as filed does not define which strand is "sense". Also, the term "sense" strand is usually defined with respect to double-stranded DNA and direction of transcription, and even then it is not always clear, especially when transcriptions from both strands proceeds in opposite directions, like in bacteria (see Ellis et al., (2001) PNAS vol. 98 no 12 pp 6742-6746, in fig. 3 on page 6744 they show direction of transcription of different genes (arrows inside the circle show direction of transcription). Hence it is not clear which of the two oligos cc or cw would correspond to sense strand of instant invention). Also see table 2 on page 6745 where strand bias in recombination at several locations is taught. Data shown for 5 different genes in Table indicates that depending on the gene either one of the single stranded oligos namely CC oligo or CW oligo gives higher number of recombinants. The question arises does "cc oligo" of prior art correspond to sense strand of instant claim or "cw oligo" of prior art corresponds to sense strand of instant claim? In other words the specification as filed does not provide adequate written description for one of ordinary skill in the art to be able to determine for any given gene which oligo corresponds to sense strand of instant claim 12.

Further instant claim 12 does not specify "target DNA". If the target is single-stranded, as in Bilang et al, (used by the examiner in the 102 rejection below), which is the "sense" strand? Therefore, the claims lack written description of a procedure in which a double-stranded DNA other than a plasmid with clearly defined transcription orientation is used.

Regarding claims 15 and 23, the specification lacks support for correcting a sequence which causes disease in any cell, nor did they describe any correcting in genomic or mitochondrial DNA.

This is a written description rejection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 12, 13, 15, 16 and 23 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for replacing bases in double-stranded phage plasmids with defined orientation of transcription in E. coli cells, does not reasonably provide enablement for replacing bases in yeast, or other eukaryotic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 12 recites "an *in vitro* base conversion method of a DNA sequence, which is a method of converting one or more bases in a target DNA sequence in a cell, consisting of preparing a single-stranded DNA fragment having 300 to 3,000 bases by cleavage from a single- stranded circular DNA, and introducing said single-stranded DNA fragment into a cell, wherein said single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence, and contains the base(s) to be converted.

The claims as recited read on *in vitro* base conversion of any cell derived from any organism with any target gene. These claims are very broad and also read on gene therapy.

The preamble of claim 12 states "in vitro" method, as the method involves cell transformation. Therefore, the method can be used to transform stem cells, for example, and then use the transformed cells for gene therapy. The specification as filed is enabled for replacing bases in double-stranded phage plasmids with defined orientation of transcription in E. coli cells, but specification as filed provides no guidance how to perform this in vitro base conversion in yeast, plants or other eukaryotic cells.

The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Liu et al. (2003) Nature Reviews Geneics vol. 4 pp 679-689 (provided by The examiner) details gene repair via recombination using single-stranded oligonucleotides, with emphasis on eukaryotic and mammalian cells. This review brings out following issues:

non-specific integration into mammalian genome (see page 680 par. 1 where for every specific homologous recombination event, there are many non- specific integration events and therein lies the most important problem--- the human cells seems to favor random rather than specific integration is taught) ,

low frequencies of homologous recombination (see page 680 par. 1 where estimates of homologous recombination is taught to be in the range of 1 in every 10^4 -10^5 cells),

destruction of single-stranded DNA inserted into mammalian cells (see page 681 par. 2 where unmodified single stranded DNA is destroyed or rendered inactive in eukaryotic cells is taught) ,

involvement of DNA repair process (See page 681 section Mode of action and applications where role of DNA repair process in homologous recombination is taught),

inconsistencies in observed strand bias of recombination efficiency and variability of results, etc (see section mode of action and application par. 1 on page 682 where non template strand (non –transcribed) strand of the target gene was found to be more amenable to gene repair is taught and in par. 2 of same page 682 its taught, there are exceptions to the non-template strand bias, which include one strain of yeast in which the template strand was favored as a target. Liu et al. go on to refer to study that beings out the variability observed in the strand bias results obtained).

Hence the review by Liu et al. clearly indicates there is a great deal of unpredictability associated with an in vitro base conversion method of a DNA sequence in bases in yeast, or other eukaryotic cells.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to perform successful efficient gene conversion using single stranded oligos in yeast plant or other eukaryotic cells. These would include devising strategies to ensure site specific integration in the mammalian gene of interest, improving efficiency of transformation of mammalian cells, improving the stability of the single stranded oligonucleotides in mammalian cells, determining in a case by case basis which strand of the double stranded DNA provides higher gene conversion efficiency, the optimal method of introducing the single stranded oligos into wide variety of eukaryotic cells such as yeast, plants and mammalian cells, efficiency of uptake of oligonucleotides by the eukaryotic cells. For an oligonucleotide based base conversion, one must also consider (a) the ability of the oligonucleotide to specifically bind the target gene; (b) formation of a stable triple complex between the oligonucleotide and the target gene (note that modification of the oligonucleotide may interfere with its ability to form stable hydrogen bonds, etc.; (c) uptake of the oligonucleotide by the cell; (d) solubility of the oligonucleotide of the cell, and other such constraints. The time table necessary to

achieve efficacious administration of effective oligonucleotides, to successfully perform in vitro base conversion for all the conceivable targets in all the various types of host cells would require a very large quantity of experimentation. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The only working example in the specification as filed teaches successful conversion of single base G to C (stop codon TGA to serine codon TCA). Here the gene to be converted is present in double stranded plasmid and the efficiency of conversion is calculated by transforming BL21 (DE3) E.coli host cells. There is no working example demonstrating conversion of any sequence present in eukaryotic genomic or mitochondrial DNA.

Guidance in the Specification.

Specification merely discloses an example where gene cloned on phagemid is used to produce sense and anti sense strand which in turn is used to transform host E.coli (prokaryotic) cells to score the rate of in vitro base conversion.

The specification provides no guidance using which one of ordinary skill in the art can determine which strand of DNA would constitute the sense strand of any given target genomic or mitochondrial gene that when used in any target cell (eukaryotic cells) would result in highly efficient in vitro gene conversion.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where one of ordinary skill in the art is provided no guidance what constitutes the sense strand of any target gene, absence of working examples where eukaryotic cells are subjected to

successful base conversions using genomic and mitochondrial genes as starting materials, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the single stranded oligonucleotides for base conversion of any target sequence in any host cell. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Since claims 13, 15, 16 and 23 depend from claim 12, they share the same problem.

This is scope of enablement rejection.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "sense" in claim 12 is a relative term which renders the claim indefinite. The term "sense" is not defined by the claim, and the since there is no definition of what the term means, and the specification does not provide a standard for ascertaining what constitutes a sense strand (see written description rejection above), and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, rendering claim 12 to be indefinite. Claims 13, 15, 16 and 23 depend from claim 12, hence all the claims 12,13, 15, 16 and 23 are indefinite.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 12, 13, 16 and 23 rejected under 35 U.S.C. 102(b) as being anticipated by Bilang et al. (1992) Molecular and Cellular Biology vol. 12 no.1 pp 329-336 (newly cited) as evidenced by Genbank accession no JA136868 which shows the hygromycin resisitance gene (hph) is 1026 bp long (newly cited)

Regarding claim 12, Bilang et al. teach: homologous recombination in *Nicotiana tabacum* (see abstract lines 2-3), by teaching homologous recombination, Bilang et al. teaches an in vitro base conversion method of a DNA sequence (see claim interpretation above),

which is a method of converting one or more bases in a target DNA sequence in a cell (see page 332 fig. 2 legend where hph-encoding gene is taught as target DNA sequence that is converted by homologous recombination) in a cell (*Nicotiana tabacum* is taught as the cell)),

consisting of preparing a single-stranded DNA fragment having 300 to 3,000 bases by cleavage from a single- stranded circular DNA (see page 330 section plasmid DNA where site-directed linearization of ssDNA circular DNA is taught. See Table 1 where oligos used for site directed cleavage of ss recombinant substrates obtained from using pBluescript vectors is taught. See Fig. 2 and legend where hph gene is shown cloned under control of CaMV35S promoter followed by polyadenylation site in constructs pTZR1 and pTZR2 that use phage replication starting at M13 inter genic region (f1) resulting in excretion of the coding i.e. complementary to mRNA, strand of hph. The full length open reading frame of hph gene is 1026 bp (see Genbank sequence accession no JA136868). Non overlapping deletion derivatives of this full length hph gene are used for homologous recombination, hence prior art teaches use of constructs that express full length single stranded circular DNA containing 1026 base long hph DNA or shorter deletion sequences. Thus cited art teaches use of 1026 or shorter hph sequences expressed as SS circular DNA, as starting point which is then linearized using oligos recited in Table 1. Since 1026 and shorter sequences fall within the range of 300 to 3,000 bases, cited art anticipates the recited limitation namely preparing a single-

stranded DNA fragment having 300 to 3,000 bases by cleavage from a single- stranded circular DNA), and

introducing said single-stranded DNA fragment into a cell (see page 329 last par. where transformation of protoplasts using ssDNA is taught. Also see page 331 Fig. 1 where result of homologous recombination performed are tabulated. Lines B of each co transformation experiment is performed with linear is shown, thus teaching introducing said single-stranded DNA fragment into a cell)

wherein said single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence and contains the base(s) to be converted (see fig. 2 legend where pTZR1 construct is taught to excrete coding strand i.e. complementary to mRNA of hph gene while pTZR2 is taught to excrete the non coding strand of hph, also see page 332 full par. 3 where The recombination frequencies of ss substrate of the same polarity (unable to anneal, class 1) were rather low and the relative recombination frequencies obtained with substrates defined as class 2 (complementary and thus could anneal directly) were high—the class 2 single stranded DNA fragment of prior art corresponds to the said single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence of instant claim, and contains the region of gene to be converted, thus teaching all the limitations of base claim 12.

Regarding claim 13, Bilang et al. teaches wherein the single-stranded circular DNA is a phagemid DNA (pTZR1 and pTZR2 see fig. 2A legend are phagemids).

Regarding claim 16, Bilang et al. teaches wherein one or more bases in a target DNA sequence in a cell of an organism are converted (see page 331 section assay for stably integrated products of intermolecular homologous recombination between ssDNA molecules and Fig. 1 panel 1 B).

Regarding claim 23, Bilang et al. teaches the target gene is present in the extruded or excreted phage DNA (extruded or excreted DNA corresponds to genomic DNA of phage f1), thereby teaching wherein the target gene is genomic DNA.

Thus Bilang et al. anticipate the subject matter recited in claims 12, 13, 16 and 23.

Conclusion

12. All claims under consideration 12, 13, 15, 16 and 23 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 6:30 am -3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suchira Pande/
Examiner
Art Unit 1637